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(54) Title: METHODS FOR PREVENTING AND TREATING BONE LOSS WITH STEROID COMPOUNDS

(57) Abstract: A method of preventing and treating abnormal metabolic bone disorders in a postmenopausal or oophorectomized woman is disclosed, which comprises administering to said an effective amount of exemestane or 17-hydro-exemestane, alone or in combination with additional therapeutic agents.



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METHODS FOR PREVENTING AND TREATING BONE LOSS WITH STEROID COMPOUNDS

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Technical field

The present invention relates to methods for modulating disrupted balance between bone resorption and bone formation in a woman with natural or induced post-menopausal. The method comprises administering to such woman in need thereof a
10 therapeutically effective amount of exemestane or 17-hydro-exemestane, either alone or in combination with a further biologically active compound. The present invention also provides pharmaceutical compositions and kits useful for carrying out these methods.

Background art

15 Human bone is constantly undergoing remodelling. The fine balance between bone resorption and bone formation is regulated by local and systemic factors and by physical forces acting on various cells including, in the bone environment, the osteoclast and the osteoblast, as well as specialised forms of the latter such as the bone lining cell and the osteocyte. However, in several metabolic bone disorders in humans and other mammals
20 including, but are not limited to, osteoporosis, periprosthetic bone loss or osteolysis, hypercalcemia of malignancy and osteolytic bone metastasis, the fine balance between osteoclast and osteoblast activity is disturbed resulting in a sustained pathological bone resorption or formation.

Osteoporosis is a systemic skeletal disease characterised by low bone mass and
25 microarchitectural deterioration of bone tissue, with a subsequent increase in bone fragility and susceptibility to fracture. Post-menopausal osteoporosis is a chronic disease which affects millions of women throughout the world and it has an enormous economical and social impact on society. Bone loss in the spine after menopause occurs at a rate of 2% per year.

30 Bone metastasis results from spreading of primary tumours to bone, where the cancer cells can interfere with the normal bone remodelling process through local regulation of osteoblast and/or osteoclast activities. This may subsequently lead to acute focal excess

of bone formation over bone resorption or vice versa as in the case of osteosclerotic and osteolytic metastasis, respectively. Breast cancer is the most frequent non-skin cancer in the female population of industrialised countries with approx. 500,000 new cases per year and 90% of those patients who die of breast cancer have bone metastases. This
5 severe prognosis makes treatment mandatory, and in most cases preventive measures are taken already at the time of identification of the primary tumour. Reduction of bone formation or resorption is believed to be an appropriate way to prevent and treat several metabolic bone diseases, including osteoporosis and osteolytic bone metastasis.

Agents such as calcitonin and bisphosphonates are able to suppress bone resorption and
10 have been used for prevention and treatment of osteoporosis and/or osteolytic bone metastasis. Furthermore, the use of steroid hormones (especially oestrogen) in hormone replacement therapy is an established prophylactic method for post-menopausal osteoporosis. However, these therapeutic agents fail to achieve satisfactory effects in some cases, due to subject limitation or uncertain efficacy, and particularly for
15 preventive medication in osteoporosis risk groups compliance is low. Furthermore, there is not yet a curative treatment for bone metastasis, and all currently used measures for bone metastatic patients are of palliative type. There is therefore need for a new prophylactic/therapeutic method for preventing and treating accentuated bone resorption in postmenopausal and oophorectomized women.

20

Disclosure of the invention

The inventors of the present invention have found that exemestane and 17-hydro-exemestane are able to modulate, and thus normalise, deranged balance between bone resorption and bone formation in a woman with natural or induced post-menopausal. In
25 this way, in particular, a reduction in progression of bone resorption and bone fragility is provided and the conditions of such patient can be improved.

This finding is surprising as exemestane and 17-hydro-exemestane are aromatase inhibitors, and in the art both non steroidal and steroidal aromatase inhibitors are known
30 to produce increased bone resorption. See, for instance Fertility and Sterility, 1998, 69/4 (709-713); Calcified Tissue International, 1996, 59/3 (179-183); J. Am. Geriatr. Soc.,

46, No. 9, S79, 1998; Journal of Bone and Mineral Research, January 2001, vol. 16, no. 1, p.89-96; and Osteoporosis, 2000,11: 637-659

Accordingly, a first object of the present invention is to provide a method for normalize
5 disrupted balance between bone resorption and bone formation, in a postmenopausal or
oophorectomized woman in need of such treatment, by administering to said woman a
therapeutically effective amount of exemestane or 17-hydro-exemestane.

A further object is to provide a method for preventing and treating abnormal metabolic
10 bone disorders in a postmenopausal or oophorectomized woman in need of such
treatment, by administering to said woman a therapeutically effective amount of
exemestane or 17-hydro-exemestane.

The term "abnormal metabolic bone disorders", as used herein, means in particular a
15 disease status wherein deranged balance between bone resorption and bone formation
causes a degree of bone resorption that exceeds the bone formation, either locally, or in
the skeleton as a whole, thus resulting in bone loss and bone fragility.

Examples of such metabolic bone disorders include, but are not limited to,
osteoporosis, periprosthetic bone loss or osteolysis, and osteolytic bone metastasis. The
20 preferred example being osteoporosis.

The invention also provide a method of using these compounds in a pharmaceutical
composition suitable therefore in the treatment of the above diseases.

25 In addition, exemestane or 17-hydro-exemestane may be used in combination therapy
with other therapeutic agents thus providing a beneficial effect on bone mass.

Accordingly, the present invention also provides a method for normalize disrupted
balance between bone resorption and bone formation, in a postmenopausal or
30 oophorectomized woman in need of such treatment, by administering simultaneously,
separately or sequentially to said woman exemestane or 17-hydro-exemestane and a

further therapeutic agent, in amounts and close in time to achieve a therapeutically useful effect.

5 A further object of the present invention is to provide a method for preventing and treating abnormal metabolic bone disorders in a postmenopausal or oophorectomized woman in need of such treatment by administering simultaneously, separately or sequentially to said woman exemestane or 17-hydro-exemestane and a further therapeutic agent, in amounts and close in time to achieve a therapeutically useful effect.

10

The term "oophorectomized" woman is meant to include both patients who underwent surgery oophorectomy and patients who underwent "medical" oophorectomy induced e.g. by GnRH agonists, for instance triptorelin, leuporelin or goserelin.

15 The term "therapeutically effective amount", according to the invention, means that amount of exemestane, 17-hydro-exemestane and, if the case, of the "further therapeutic agent" that is able to elicit "a therapeutically useful effect". Namely an amount that is able to normalise deranged balance between bone resorption and bone formation. The term "normalise", as used herein, in particular is therefore meant a method of slowing, 20 stopping or inhibiting bone resorption, and recovering bone formation.

The term "close in time to achieve a therapeutically useful effect " means a combined administration schedule of exemestane or 17-hydro-exemestane and the "further therapeutic agent" that is able to elicit "a therapeutically useful effect". Preferably 25 exemestane or 17-hydro-exemestane and the "further therapeutic agent" are administered during the same day in either order.

The invention also provides the use of exemestane or 17-hydro-exemestane in the manufacture of a medicament for normalize disrupted balance between bone resorption 30 and bone formation, in a postmenopausal or oophorectomized woman.

A further object of the present invention is to the use of exemestane or 17-hydro-exemestane in the manufacture of a medicament for preventing and treating abnormal metabolic bone disorders in a postmenopausal or oophorectomized woman

- 5 The present invention also provides the use of exemestane or 17-hydro-exemestane in the manufacture of a medicament for preventing and treating abnormal metabolic bone disorders in a postmenopausal or oophorectomized woman undergoing a simultaneous, separate or sequential treatment with another therapeutic agent.
- 10 The combination preparation according to the invention can also include combination packs or compositions in which the constituents are placed side by side and can be administered simultaneously, separately or sequentially to one and the same woman. Accordingly, exemestane, 17-hydro-exemestane and the additional therapeutic agent may be present within a single or distinct container.
- 15 The inventors of the present invention have also found that prevention and control of the above mentioned disorders by combined administration of a therapeutically effective amount of exemestane or 17-hydro-exemestane and a therapeutically effective amount of a further therapeutic agent, can produce a therapeutic effect which is greater
- 20 than that obtainable by single administration of a therapeutically effective amount of either sole exemestane or 17-hydro-exemestane or the sole "additional" therapeutic agent. Namely, such combined therapy provides a synergistic or superadditive therapeutic effect.
- 25 Most importantly, they have found that such newly obtained therapeutic effect is not paralleled by the toxic effects, otherwise caused by single administration of either therapeutically effective amounts of exemestane, 17-hydro-exemestane or of the "additional" therapeutic agent.
- 30 Product exemestane is compound 6-methylenandrost-1,4-diene-3,17-dione which is known for instance from US Pat. No. 4,808,616. Product 17-hydro-exemestane is

compound 6-methylenandrost-1,4-diene-17 β -ol-3-one, which is an active metabolite of exemestane and is known from EP 307135.

Compound 6-methylenandrost-1,4-diene-17 β -ol-3-one, if desired, can be salified with a pharmaceutically acceptable base, as described in EP 307135, in particular as sodium or potassium salt. However, for convenience, the term "17-hydro-exemestane", as used
5 herein, refers to such compound both as a free alcohol and as a pharmaceutically acceptable salt thereof.

The "additional" therapeutic agent, for combination therapy with exemestane or 17-hydro-exemestane of the above mentioned bone disorders, is for instance an agent
10 selected from the group consisting of a selective estrogen receptor modulator (SERM), an $\alpha\text{v}\beta 3$ inhibitor or antagonist, a vitamin D or a vitamin D derivative, sodium fluoride, a COX-2 inhibitor and a biphosphonate compound, or a mixture thereof.

15 A therapeutic agent mixture, according to the invention, which can be administered in combination with exemestane or 17-hydro-exemestane can comprise one or more, preferably 2 to 4, in particular 2 to 3, therapeutic agents as defined above.

A vitamin D is e.g. ergocalciferol or cholecalciferol. A vitamin D derivative is e.g. 1,25-dihydrocalciferol (calcitrol) or Roche Bioscience compound Ro-26-9228.
20

A selective estrogen receptor modulator (SERM) is for instance raloxifene, tamoxifen, toremifene, arzoxifene, idoxifene, fulvestrant, droloxifene and Universite Laval compound EM-800 i.e. propanoic acid, 2,2-dimethyl-4-[(2S)-7-(2,2-dimethyl-1-oxopropoxy)-4-methyl-2-[4-[2-(1-piperidinyl)ethoxy]phenyl]-2H-1-benzopyran-3-yl]phenyl ester.
25

An $\alpha\text{v}\beta 3$ integrin inhibitors or antagonists is for instance selected from Vitaxin antibody (Ixsys); cilengitide i.e. (cyclo[RGDF-N(Me)V-] (Merck); GlaxoSmithKline compound SB-273005; Aventis compound HMR 1392; Merck compound L 806977;
30 (10S)-10,11-dihydro-3-[3-(2-pyridinylamino)propoxy]-5H-dibenzo[a,d]cycloheptene-10-acetic acid;

(2S)-7-[[[(1H-benzimidazol-2-ylmethyl)methylamino]carbonyl]-2,3,4,5-tetrahydro-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid;

(2S)-2,3,4,5-tetrahydro-4-methyl-7-[[[(5-methyl-1H-imidazo[4,5-b]pyridin-2-yl)methyl]amino]carbonyl]-3-oxo-1H-1,4-benzodiazepine-2-acetic acid;

- 5 (bR)-b-[[[(3R)-2-oxo-3-[2-(5,6,7,8-tetrahydro-[1,8]-naphthyridin-2-yl)ethyl]1-1-pyrrolidinyl]acetyl]amino]-d-(1H-indol-3-yl)pentanoic acid; and
(3R)-N-[3-hydroxy-5-[(1,4,5,6-tetrahydro-5-hydroxy-2-pyrimidinyl)amino]benzoyl]-glycyl-3-(3-bromo-5-chloro-2-hydroxyphenyl)-b-alanine (compound SD 7784); or a mixture thereof.

10

- A biphosphonate compound is for instance selected from alendronic acid, alendronate, cimadronate, clodronoc acid, clodronate, Leo Pharmaceutical Products compound EB-1053, etidronic acid, etidronate, ibandronate, neridronate, olpadronate, pamidronate, piridronate, risedronate, tiludronate and zolendronate or a pharmaceutically acceptable
15 salt thereof and mixtures thereof. Preferably it is selected from alendronate, cimadronate, clodronate, tiludronate, etidronate, ibandronate, neridronate, risedronate, piridronate, pamidronate and pamidronate or a pharmaceutically acceptable salt thereof. In particular from alendronate, pamidronate, clodronate, ibandronate, risedronate and pamidronate or a pharmaceutically acceptable salt thereof and mixtures thereof. These
20 compounds are known for instance from WO 01/15703.

A COX-2 inhibitor is for instance celecoxib, rofecoxib, parecoxib and valdecoxib, in particular celecoxib.

25 PHARMACOLOGY

The therapeutic effect of exemestane and 17-hydro-exemestane, in preventing and treating abnormal metabolic bone disorders, according to the present invention, is shown for instance by the following biological activity test data.

30 Effects of exemestane on bone in the ovariectomized rat.

The purpose of this study was to evaluate the effects of exemestane on bone in cycling and ovariectomized (OVX) rats.

Methods:

10-month-old Sprague-Dawley female rats were sorted into following experimental groups each of 14 -16 animals: intact control, OVX control, OVX plus exemestane (by weekly intramuscular injection with dose 100 mg/kg). After 16 weeks of treatment, all rats were euthanized. Blood samples were collected from overnight fasted animals. The femora and whole lumbar spine were removed at necropsy and scanned by dual energy x-ray absorptiometry. The bone mineral density (BMD) of each left femur and lumbar spine were measured. Bone resorption biomarker pyridinoline (Pyd) was measured by competitive enzyme immunoassay using the Pyd crosslink kit obtained from Metra Biosystem, Inc., USA.

Results:

- 1) After 16 weeks of treatment, the BMD of the lumbar spine was 11% lower in OVX control rats than in intact controls ($P < 0.0001$). The OVX animals given exemestane had 99% of the BMD value observed in intact rats, the BMD value being significantly higher than those of OVX control rats ($P < 0.0001$). Similar effects were observed on femoral BMD.
- 2) The serum Pyd excretion was 41% higher in OVX controls than in intact controls ($P < 0.0001$), thus suggesting a excessive bone resorption in OVX rats. The OVX animals given exemestane reduced the OVX-induced increase of Pyd by 29% ($P < 0.0001$) thus suggesting a prevention of bone resorption.

Conclusion:

The present data show the potent effect of exemestane in preventing bone loss. Therefore, exemestane and 17-hydro-exemestane are expected to be useful in preventing and treating abnormal metabolic bone disorders in a postmenopausal or oophorectomized woman, in particular, undergoing adjuvant cancer therapy or chemoprevention.

Method and Administration

In effecting treatment of a patient in a therapy/prophylactic method according to the invention, exemestane, 17-hydro-exemestane and, if the case, the other therapeutic agent can be administered in any form or mode which makes the compounds bioavailable in therapeutically effective amounts, including oral, parenteral and rectal

routes.

By the term "administered" or "administering" as used herein is meant any acceptable manner of administering a drug to a patient which is medically acceptable including parenteral, oral and rectal administration.

- 5 By "parenteral" is meant intravenous, subcutaneous, intra-nasal, pulmonary, intradermal or intramuscular administration.

Oral administration includes administering exemestane, 17-hydro-exemestane or, if the case, the constituents of the combined preparation in a suitable oral form such as, e.g., tablets, capsules, suspensions, solutions, emulsions, powders, syrups and the like.

- 10 The actual preferred method and order of administration of the combined preparations of the invention may vary according to, inter alia, the particular pharmaceutical formulation of exemestane or 17-hydro-exemestane being utilized, the particular pharmaceutical formulation of the additional therapeutic being utilized, the particular metabolic bone disorder to be prevented or treated and the particular patient being
15 treated.

- In the combined method of prevention or treatment according to the subject invention, exemestane or 17-hydro-exemestane, respectively, may thus be administered simultaneously or concomitantly with the further therapeutic agent or the compounds may be administered sequentially, in either order. Preferably the compounds are
20 administered concomitantly during the same day in either order.

Dosage

- The dosage ranges for the administration of exemestane, 17-hydro-exemestane and, if the case, the additional therapeutic agent in order to achieve a therapeutically useful effect may vary with the age, condition and extent of the disease in the patient and can
25 be determined by one of skill in the art.

The dosage regimen must therefore be tailored to the particular of the patient's conditions, response and associate treatments in a manner which is conventional for any therapy, and may need to be adjusted in response to changes in conditions and/or in light of other clinical conditions.

- 30 According to the method provided the present invention, exemestane for instance can be administered orally in a dosage range varying from about 2.5 mg daily to about 600 mg daily, in particular from about 10 to about 50, more preferably from about 10 to about

25 mg daily, or parenterally in a dosage ranging from about 50 to about 500 mg per injection.

17-hydro-exemestane for instance can be administered orally in a dosage range varying from about 0.25 to about 100 mg, in particular from about 0.5 mg daily to about 50 mg ,
5 more preferably from about 1 to about 5 mg daily, or parenterally in a dosage ranging from about 5 to about 50 mg per injection.

The effective therapeutic amounts of the further therapeutic agents to be used in combination with exemestane or 17-hydro-exemestane, respectively according to the invention, are in general those commonly used in therapy for such compounds. More
10 specifically, a therapeutically effective amount of another therapeutic agent means an amount of a compound, which when administered in combination with exemestane or 17-hydro-exemestane, is effective to prevent or treat abnormal metabolic bone disorders, as herein defined. Such amount is well within the capability of those skilled in the art.

15 As to vitamin D and vitamin D derivative, for instance 1,25-dihydrocalciferol (calcitrol) can be administered in amounts ranging from about 0.20 to about 0.30 mcg/day or any other day , in particular from 0.25 to 0.5 mcg day.

As to sodium fluoride, for instance an amount ranging from about 0.5 to about 2.5 mg/day can be administered.

20 As to $\alpha\text{v}\beta 3$ integrin inhibitors or antagonists, for instance an effective amount of compound SD 7784 is from about 10 to about 300 mg/kg, preferably per os, in particular from about 20 to about 200 mg/kg.

A selective estrogen receptor modulator (SERM) can be administered in a dosage according to the common practice, e.g. in a dosage of about 0.1 to about 30 mg/Kg body
25 weight per day.

An effective amount of tamoxifen may be in the range of about 10 to about 40 mg/day.

An effective amount of fulvestrant may be in the range of about 50 mg to about 300mg/day i.m., in particular of about 100 to about 250 mg/day i.m.

An effective amount of raloxifen may be in the range of about 5 to about 350 mg/day, in
30 particular about 60 mg/day.

A biphosphonate compounds, for instance alendronate can be administered at a dosage ranging from about 3 mg to about 250 mg, depending on dosing interval, in particular from about 5 to about 20 mg/day.

An effective amount of a COX-2 inhibitor may be in the range of about 0.1 to about 5 2000 mg, preferably in the range of about 0.5 to about 500 and most preferably between about 1 and about 200 mg. In particular as to celecoxib, rofecoxib, parecoxib and valdecoxib, a daily dosage of about 0.01 to about 100 mg/Kg body weight, preferably between about 0.1 and about 50 mg/Kg body weight may be appropriate. The daily dosage can be administered in one to four doses per day.

10 More particularly, as to celecoxib a dosage from about 50 to about 500 mg, in particular about 200 mg, once or twice a day may be appropriate.

As to rofecoxib the dosage normally ranges from about 12.5 to about 50 mg/day. The route of administration is preferably systemic e.g. oral or parenteral, in particular intravenous or intramuscularly.

15 A pharmaceutically composition containing exemestane and/or another therapeutic agent according to the invention can be prepared according to well known techniques to those skilled in the art.

For instance a pharmaceutical composition containing exemestane or 17-hydro-exemestane can be prepared according to US 4,808,616 or EP 307135, respectively.

CLAIMS

1. Method for normalising disrupted balance between bone resorption and bone formation, in a postmenopausal or oophorectomized woman in need of such treatment,
5 the method comprising administering to said woman a therapeutically effective amount of exemestane or 17-hydro-exemestane.

2. Method for preventing and treating abnormal metabolic bone disorders in a postmenopausal or oophorectomized woman in need of such treatment, the method
10 comprising administering to said woman a therapeutically effective amount of exemestane or 17-hydro-exemestane.

3. Method for normalising disrupted balance between bone resorption and bone formation, in a postmenopausal or oophorectomized woman in need of such treatment,
15 the method comprising administering simultaneously, separately or sequentially to said woman exemestane or 17-hydro-exemestane and a further therapeutic agent, in amounts and close in time to achieve a therapeutically useful effect.

4. Method for preventing and treating abnormal metabolic bone disorders in a postmenopausal or oophorectomized woman in need of such treatment, the method
20 comprising administering simultaneously, separately or sequentially to said woman exemestane or 17-hydro-exemestane and a further therapeutic agent, in amounts and close in time to achieve a therapeutically useful effect.

25 5. Method, according to claim 2 or 4, wherein the abnormal metabolic bone disorder is selected from osteoporosis, periprosthetic bone loss or osteolysis, and osteolytic bone metastasis.

6. Method, according to claim 2 or 4, wherein the abnormal metabolic bone
30 disorder is osteoporosis.

7. Method, according to claim 2 or 4, wherein exemestane is administered orally in an amount ranging from about 2.5 mg to about 600 mg daily.

8. Method according to claim 2 or 4, wherein exemestane is administered orally
5 in an amount ranging from about 10 mg to about 50 mg daily.

9. Method according to claim 2 or 4, wherein exemestane is administered orally in an amount ranging from about 10 mg to about 25 mg daily.

10. Method according to claim 2 or 4, wherein exemestane is administered parenterally in an amount ranging from about 50 mg to about 500 mg.

11. Method according to claim 2 or 4, wherein 17-hydro-exemestane is administered orally in an amount ranging from about 0.25 mg to about 100 mg daily.

12. Method according to claim 2 or 4, wherein 17-hydro-exemestane is administered orally in an amount ranging from about 0.5 mg to about 50 mg daily.

13. Method according to claim 2 or 4, wherein 17-hydro-exemestane is
20 administered orally in an amount ranging from about 1mg to about 5mg daily.

14. Method according to claim 2 or 4, wherein 17-hydroxy-exemestane is administered parenterally in an amount ranging from about 5 mg to about 50 mg.

25 15. Method according to claim 4, wherein the additional therapeutic agent is selected from the group consisting of a selective estrogen receptor modulator (SERM), an α v β 3 inhibitor or antagonist, a vitamin D or a vitamin D derivative, sodium fluoride, a COX-2 inhibitor and a biphosphonate compound, or a mixture thereof.

30 16. Method according to claim 15, wherein the SERM is selected from the group consisting of raloxifene, tamoxifen, toremifene, arzoxifene, idoxifene; propanoic acid, 2,2-dimethyl-4-[(2S)-7-(2,2-dimethyl-1-oxopropoxy)-4-methyl-2-[4-[2-(1-

piperidinyloxy]phenyl]-2H-1-benzopyran-3-yl]phenyl ester (EM 800); fulvestrant and droloxifene.

17. The method according to claim 15, wherein the $\alpha\beta$ 3 integrin inhibitor or
5 antagonist is selected from the group consisting of: Vitaxin antibody (Ixsys); cilengitide
i.e. (cyclo[RGDf-N(Me)V-] (Merck); GlaxoSmithKline compound SB-273005; Aventis
compound HMR 1392; Merck compound L 806977;
(10S)-10,11-dihydro-3-[3-(2-pyridinylamino)propoxy]-5H-dibenzo[a,d]cycloheptene-
10-acetic acid;
10 (2S)-7-[[[(1H-benzimidazol-2-ylmethyl)methylamino]carbonyl]-2,3,4,5-tetrahydro-4-
methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid;
(2S)-2,3,4,5-tetrahydro-4-methyl-7-[[[(5-methyl-1H-imidazo[4,5-b]pyridin-2-
yl)methyl]amino]carbonyl]-3-oxo-1H-1,4-benzodiazepine-2-acetic acid;
(bR)-b-[[[(3R)-2-oxo-3-[2-(5,6,7,8-tetrahydro-[1,8]-naphthyridin-2-yl)ethyl]1-1-
15 pyrrolidinyl]acetyl]amino]-d-(1H-indol-3-yl)pentanoic acid; and
(3R)-N-[3-hydroxy-5-[(1,4,5,6-tetrahydro-5-hydroxy-2-pyrimidinyl)amino]benzoyl]-
glycyl-3-(3-bromo-5-chloro-2-hydroxyphenyl)-b-alanine (compound SD 7784); or a
mixture thereof.

- 20 18. The method according to claim 15, wherein a vitamin D is ergocalciferol or
cholecalciferol and a vitamin D derivative is 1,25-dihydrocalciferol (calcitrol) or Roche
Bioscience compound Ro-26-9228.

19. The method according to claim 15, wherein the biphosphonate compound is
25 selected from alendronic acid, alendronate, cimadronate, clodronoc acid, clodronate,
Leo Pharmaceutical Products compound EB-1053, etidronic acid, etidronate,
ibandronate, neridronate, olpadronate, pamidronate, piridronate, risedronate, tiludronate
and zolendronate; or a pharmaceutically acceptable salt thereof; and mixtures thereof.

- 30 20. Method, according to claim 15, wherein the COX-2 inhibitor is selected
from celecoxib, rofecoxib, parecoxib and valdecoxib.

21. Use of exemestane or 17-hydro-exemestane in the manufacture of a medicament for modulating disrupted balance between bone resorption and bone formation, in a postmenopausal or oophorectomized woman.

5 22. Use of exemestane or 17-hydro-exemestane in the manufacture of a medicament for preventing and treating abnormal metabolic bone disorders in a postmenopausal or oophorectomized woman.

10 23. Use of exemestane or 17-hydro-exemestane in the manufacture of a medicament for preventing and treating abnormal metabolic bone disorders in a postmenopausal or oophorectomized woman undergoing a simultaneous, separate or sequential treatment with a further therapeutic agent.

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Declaration under Rule 4.17:

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for all designations*

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4 September 2003

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: METHODS FOR PREVENTING AND TREATING BONE LOSS WITH STEROID COMPOUNDS

(57) Abstract: A method of preventing and treating abnormal metabolic bone disorders in a postmenopausal or oophorectomized woman is disclosed, which comprises administering to said an effective amount of exemestane or 17-hydro-exemestane, alone or in combination with additional therapeutic agents.

WO 03/032961 A3

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 02/11123

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/568 A61K31/5685 A61K45/06 A61P19/08 A61P19/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BIOSIS, MEDLINE, SCISEARCH, CHEM ABS Data, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
X	WO 01 12206 A (SCHMIDT ALFRED ;WIELAND HEINRICH (DE)) 22 February 2001 (2001-02-22)	1-14, 21-23
Y	page 1, line 6 - line 21 page 6, line 26 -page 7, line 10 page 8, line 13 -page 9, line 16 page 15, line 11 - line 22 page 19, line 1 - line 20 page 20, line 30 -page 21, line 5 page 29, line 11 -page 30, line 16 claims 1-3,13,16 --- -/--	1-14, 21-23



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date.
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search

3 Apr11 2003

Date of mailing of the international search report

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Cielen, E

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/EP 02/11123

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 307 135 A (ERBA CARLO SPA) 15 March 1989 (1989-03-15) cited in the application page 2, line 22 - line 23 page 3, line 54 - line 55 page 7, line 50 - line 51 page 8, line 5 - line 53 example 1 ---	1-14, 21-23
A	WO 00 02553 A (LIPOGENICS INC) 20 January 2000 (2000-01-20) page 1, line 6 - line 11 page 2, line 7 - line 19 page 10, line 17 -page 11, line 2 claims 11,12 ---	15,16, 18,19
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A	PYTLIK M ET AL: "Effects of formestane on development of osteopenia caused by ovariectomy in rats." CALCIFIED TISSUE INTERNATIONAL, vol. 64, no. SUPPL. 1, 1999, page S68 XP008012825 XXVith European Symposium on Calcified Tissues;Maastricht, Netherlands; May 7-11, 1999 ISSN: 0171-967X the whole document ---	1,2,5, 21,22

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 02/11123

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	<p>ZILEMBO N ET AL: "Markers of bone turnover in metastatic breast cancer (MBC) patients having progressed on tamoxifen: Short term effect of further treatment with either exemestane (EXE) or megestrol acetate (MA)."</p> <p>EUROPEAN JOURNAL OF CANCER, vol. 37, no. Supplement 6, 23 October 2001 (2001-10-23), pages S193-S194, XP001133767</p> <p>11th European Cancer Conference;Lisbon, Portugal; October 21-25, 2001, October, 2001</p> <p>ISSN: 0959-8049</p> <p>the whole document</p>	1-4,7-9, 15,16, 21-23
P,X	<p>GOSS PAUL: "Anti-aromatase agents in the treatment and prevention of breast cancer."</p> <p>CANCER CONTROL, (2002 MAR-APR) 9 (2 SUPPL) 2-8. REF: 28 ,</p> <p>XP001133770</p> <p>abstract</p> <p>page 3, column 2, paragraph 2 - paragraph 3</p> <p>page 6, column 1, paragraph 1</p>	1,2,21, 22
P,X	<p>GOSS P ET AL: "The effects of exemestane on bone and lipids in the ovariectomized rat."</p> <p>BREAST CANCER RESEARCH AND TREATMENT, vol. 69, no. 3, October 2001 (2001-10), page 224 XP008012823</p> <p>24th Annual San Antonio Breast Cancer Symposium;San Antonio, Texas, USA; December 10-13, 2001, October, 2001</p> <p>ISSN: 0167-6806</p> <p>the whole document</p>	1,2,5, 10,21,22

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 02/11123

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 1-20 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 02/11123

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